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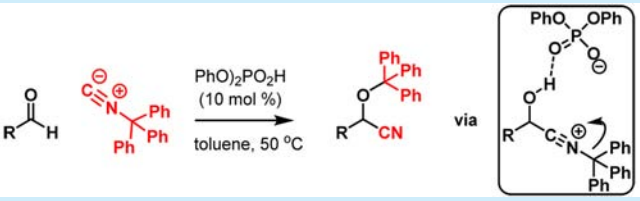
Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide

Răzvan C. Cioc, Peter Schuckman, Hans D. Preschel, Tjøstil Vlaar, Eelco Ruijter,* and Romano V. A. Orru*

Department of Chemistry & Pharmaceutical Sciences and Amsterdam Institute for Molecules Medicines and Systems (AIMMS), Vrije Universiteit Amsterdam, De Boelelaan 1108, 1081 HZ Amsterdam, the Netherlands

Ⓢ *Supporting Information*

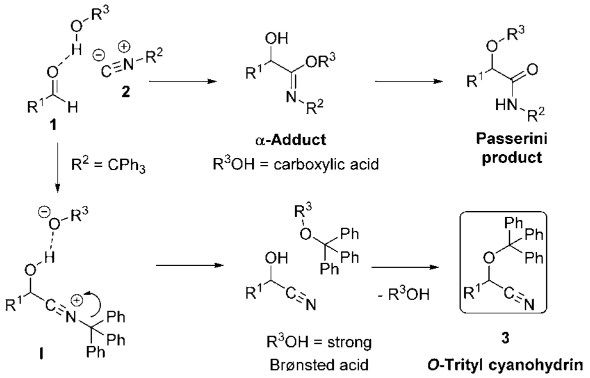
ABSTRACT: Cyanohydrins are versatile intermediates toward valuable organic compounds like α-hydroxy carboxylic acids, α-amino acids, and β-amino alcohols. Numerous protocols are available for synthesis of (O-protected) cyanohydrins, but all procedures invariably rely on the use of toxic cyanide sources. A novel cyanide-free synthesis of *O*-trityl protected cyanohydrins via a catalytic Passerini-type reaction involving aldehydes and trityl isocyanide is reported. The feasibility of a catalytic asymmetric reaction is demonstrated using chiral phosphoric acid catalysis.



The cyanohydrin functionality is often encountered in biologically active compounds[1] and represents a versatile handle for further synthetic elaboration, e.g., into α-hydroxy carboxylic acids, β-amino alcohols, and α-amino acids. Cyanohydrin formation by nucleophilic addition of cyanide to carbonyl compounds is a key C−C bond forming process frequently employed in the synthesis of natural products, pharmaceuticals, and agrochemicals.[2] Consequently, this chemical transformation has received considerable attention, and numerous protocols have been developed to access cyanohydrins and their O-protected derivatives, which are usually more stable and more convenient to manipulate. However, these methods invariably rely on highly toxic cyanide sources (HCN, metal cyanides, TMSCN, cyanoformate esters, cyanophosphate esters, etc.) and often undesirable metal catalysts. Notably, the (bio)catalytic enantioselective synthesis of cyanohydrin derivatives, which has seen remarkable progress in the past decade,[3] suffers from similar drawbacks as all protocols employ toxic cyanide reagents as well.

Recently, we showed that triphenylmethyl (trityl) isocyanide **2** can function as cyanide donor in Strecker reactions following an interrupted Ugi reaction pathway, i.e., the C−N fragmentation of the key *N*-trityl nitrilium ion intermediate.[4] As trityl isocyanide is a readily available, hydrolytically stable[5] crystalline solid, we consider this reagent a viable benign alternative to traditional cyanide sources.[6] We thus investigated the utility of **2** in the synthesis of cyanohydrin derivatives **3** via an interrupted Passerini-type mechanism, in which the cyanohydrin functionality is generated upon addition of trityl isocyanide to activated aldehyde **1** and subsequent fragmentation of the resulting *N*-trityl nitrilium ion intermediate **I**. (Scheme 1). This mechanism confers an important advantage in the synthesis of cyanohydrins as both the hazardous handling of cyanide reagents and the generation of toxic cyanide species in solution can be avoided.

Scheme 1. Interrupted Passerini-Type Reaction



Additionally, instead of conventional transition metal catalysis, this process relies on simple Brønsted acid catalysis, which to the best of our knowledge has not been applied before in cyanohydrin synthesis.[7]

We began our optimization using isovaleraldehyde as the benchmark substrate. Initial experiments revealed two important observations: (i) we indeed found the desired reactivity, interestingly with concomitant tritylation of the free cyanohydrin product; (ii) the major competitive pathway was the isomerization of trityl isocyanide **2** to triphenyl acetonitrile **2b** (see mechanistic discussion).[8] Both these events indicated the presence of the trityl cation as a reactive intermediate, validating our preliminary mechanistic hypothesis. A small screen of Brønsted acids established diphenyl phosphate (DPP) as the optimal catalyst for the reaction (see Supporting Information for details). The reaction performed best in toluene while other

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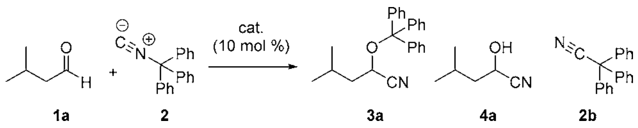
solvents gave (moderate) selectivity for the free cyanohydrin **4a**.[9] We considered the *O*-trityl protected derivative **3a** the more interesting target[10] and pursued the optimization for this product. Notably, increased temperatures (50 or 70 °C) were beneficial for the yield (Table 1, entry 6) as was the use of normal grade solvent instead of rigorously dry conditions (Table 1, entries 9–11). Finally, satisfactory conversion and selectivity were obtained by diluting the reaction solution to a 0.125 M solution in combination with heating at 50 °C (Table 1, entry 11).

Table 1. Optimization of Reaction Conditions[a]



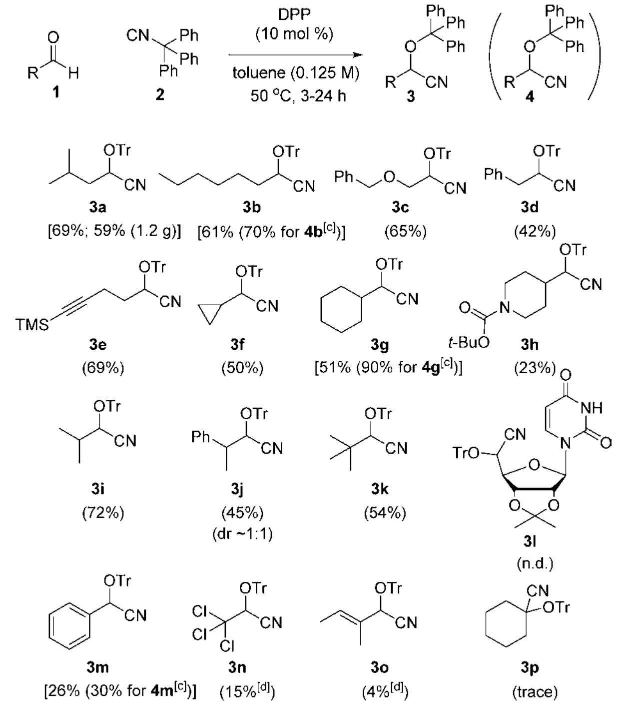
entry	temp (°C)	concn (M)	1/2	time (h)	yield[b] (%)	3a/4a
1	rt	0.25	1:1.1	24	0	0
2	rt	0.25	1:1.1	24	74	61:13
3	0	0.25	1:1.1	24	70	53:17
4	rt	0.25	2:1	24	71	67:4
5	rt	0.25	1:2	24	75	69:6
6	50	0.25	1:1.1	5	79	72:7
7	70	0.125	1:1.1	2	84	79:5
8[c]	50	0.125	1:1.1	5	79	72:7
9[d]	50	0.125	1:1.1	5	91	53:38
10[e]	50	0.125	1:1.1	5	65	57:8
11	**50**	**0.125**	**1:1.1**	**5**	**85**	**79:6**

[a]Standard conditions: isovaleraldehyde (0.25 mmol) in toluene, DPP (10 mol %), and trityl isocyanide (1.1 equiv) stirred at the indicated temperature for 2–24 h (isocyanide conversion monitored with TLC). [b]Combined yield of **3a** and **4a** based on NMR analysis with mesitylene as internal standard. [c]Using freshly distilled toluene and inert conditions. [d]With addition of 3 Å molecular sieves. [e]With addition of MgSO$_4$.

With this optimized protocol, we explored the scope of aldehydes in the reaction. Aliphatic aldehydes with a range of diverse substitution patterns (linear, branched, α-heteroatom substituted, etc.) underwent cyanotritylation with good efficiency. Benchmark isovaleraldehyde **1a** yielded 69% desired product (59% on gram scale) after chromatographic purification. Phenylacetaldehydes **1d** and **1j** gave somewhat reduced yields of the corresponding cyanotritylation products presumably due to side reactions arising from their propensity to enolize under acidic conditions. Similarly, N-Boc-derivative **3h** most likely undergoes Boc deprotection under the reaction conditions, leading to a basic site that quenches the catalyst. Hence the desired product was obtained in low yield compared to the structurally related product **3g**. Notably, bulky aldehydes are well tolerated (pivalaldehyde, **1k**). A complex reaction mixture that hampered the isolation of the desired product was observed for the highly functionalized input **1l**, whereas aromatic aldehydes performed modestly due to extensive conversion of trityl isocyanide to triphenylacetonitrile. This behavior was also observed for chloral (**1n**). Finally, α,β-unsaturated aldehydes (tiglic aldehyde, **1o**) and ketones (cyclohexanone, **1p**) proved incompatible substrates due to their reduced electrophilicity.

Deprotection to free cyanohydrins is straightforward (stirring for 1 h at rt in TFA with 1 equiv of Et$_3$SiH) and can be performed in the same pot, without intermediate purification of the tritylated product (as shown for **4b**, **4g**, and **4m**). This protocol is simpler and higher yielding[11] than the sequential cyanotritylation-detritylation since it includes minor amounts of **4** resulting from the first step (up to 10%) and circumvents purification issues of **3**.[12]

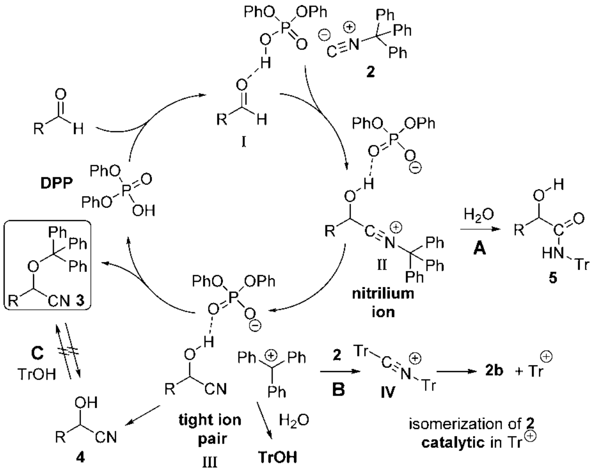
Table 2. Reaction Scope[a,b]



[a]Standard conditions: aldehyde (0.5 mmol) in toluene (0.125 M), DPP (10 mol %), and trityl isocyanide (1.1 equiv) stirred at 50 °C for 2–24 h (isocyanide conversion monitored with TLC). [b]Isolated yields for *O*-trityl cyanohydrins **3**. [c]Isolated yield for free cyanohydrin **4** after deprotection with TFA–Et$_3$SiH without purification of **3**. [d]Yield based on NMR analysis with internal standard.

The observations made during the reaction optimization and the evaluation of the substrate scope allowed us to draw the following mechanistic picture (Scheme 2). The aldehyde activated by DPP[13] **I** undergoes nucleophilic addition by trityl isocyanide leading to nitrilium ion intermediate **II**. This key intermediate fragments at the labile N-Tr bond into the free cyanohydrin **4** and the reactive trityl cation, which combine to

Scheme 2. Proposed Reaction Mechanism

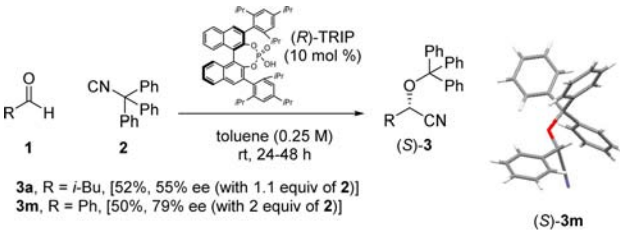


afford the final product **3** and regenerate the catalyst. The trityl group transfer is an essential step and deserves additional comment. Most likely, this process occurs from a tight ion pair, **III**;[14] control experiments showed that product **3** cannot be formed by tritylation of the free cyanohydrin **4** with triphenylmethanol (TrOH) under the reaction conditions (pathway C).[15] On the other hand, the reaction between **4a** and the covalent compound diphenyl trityl phosphate (essentially intermediate **III**) is complete within minutes at room temperature.[14,16] If the trityl cation diffuses in solution, it initiates isomerization of trityl isocyanide to trityl cyanide **2b** via an ionic chain mechanism involving nitrilium ion intermediate **IV** (pathway **B**). Since this unproductive consumption of trityl isocyanide is catalytic in the trityl cation, it represents an important limiting factor for the reaction. This becomes particularly problematic with inputs for which the trityl transfer to the free cyanohydrin is more difficult due to reduced nucleophilicity (benzaldehyde, chloral, see Table 2) or steric factors (**1p**). Notably, the reaction performs better if traces of water are present, since the trityl cation is rapidly quenched and the extent of isomerization of **2** is reduced.[17] Indeed, when the reaction is run with the addition of 0.5 equiv of water, no isomerization is detected; interestingly, α-hydroxyamide **5** is also observed (7% crude NMR yield, 9% selectivity). The selectivity for **5** (which is the product of the capture of nitrilium ion **II** by water) is enhanced at rt compared to 50 °C (35% vs 9%) plausibly because the rate of the fragmentation pathway (**II** → **III**) shows stronger temperature dependence compared to the alternative addition of water (pathway **A**).[18]

An alternative mechanism based on tritylium Lewis acid catalysis[14,19] can also be imagined, but since trityl isocyanide is rapidly isomerized in the presence of traces of the trityl cation, this pathway is unlikely. Similarly, a mechanism involving fragmentation of the isocyanide prior to the addition (protonation of **2** and release of HCN to add to **1**) can be ruled out as the isocyanide is essentially stable under the reaction conditions.[20] The experimental data are in good agreement with the Passerini/fragmentation mechanism, which implies that this novel approach toward cyanohydrins is essentially cyanide-free.

With this knowledge, we attempted the asymmetric synthesis of *O*-tritylated cyanohydrins using chiral phosphoric acid (CPA) catalysis. In the past decade, CPAs have been extensively employed as catalysts for an impressive array of asymmetric transformations.[21] However, reactions involving isocyanides as reagents are rare: to the best of our knowledge, there are only two reports describing asymmetric Passerini-type chemistry under CPA catalysis.[22] As a proof of concept, the reaction with (*R*)-TRIP as the catalyst affords enantioenriched cyanohydrin derivatives **3a** and **3m** in good yields and reasonable ee's as shown in Scheme 3.[23] Interestingly, TRIP performed slightly better in terms of yield and selectivity than DPP,[24] and (*S*)-*O*-trityl mandelonitrile **3m** could be obtained in good yield and with 79% ee. Further optimization is currently underway in our laboratories.

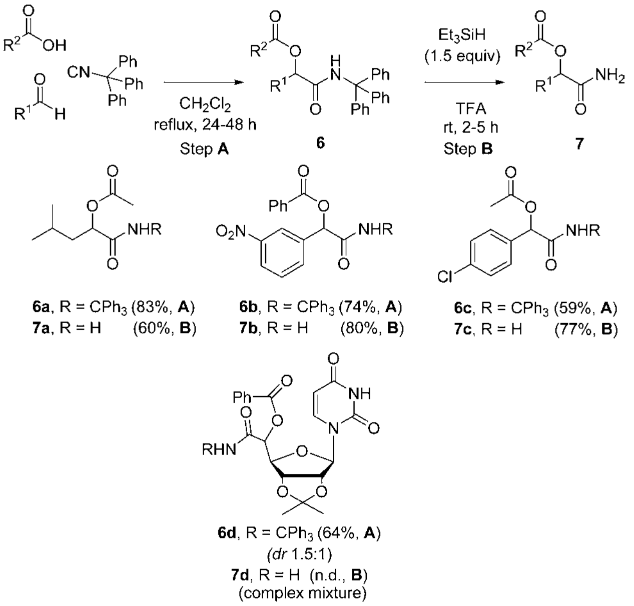
Scheme 3. Enantioenriched *O*-Trityl Cyanohydrins



3a, R = *i*-Bu, [52%, 55% ee (with 1.1 equiv of **2**)]
3m, R = Ph, [50%, 79% ee (with 2 equiv of **2**)]

Having established trityl isocyanide as a reagent that stands out in its class, we pursued the more conventional Passerini three-component reaction involving **2**, an aldehyde, and a carboxylic acid. This reaction is mechanistically closely related to the DPP-catalyzed cyanohydrin synthesis (nucleophilic addition of the isocyanide to the acid-activated aldehyde as the initiating event, see Scheme 1), and thus chemoselectivity is an important issue here. Remarkably, the Passerini reaction with trityl isocyanide proceeds with complete selectivity for the α-acyloxyamides **6** with all possible combinations of inputs (aromatic/aliphatic aldehyde and carboxylic acid, Scheme 4).

Scheme 4. Scope of Passerini−Deprotection Sequence



6a, R = CPh_3 (83%, **A**)
7a, R = H (60%, **B**)

6b, R = CPh_3 (74%, **A**)
7b, R = H (80%, **B**)

6c, R = CPh_3 (59%, **A**)
7c, R = H (77%, **B**)

6d, R = CPh_3 (64%, **A**)
(*dr* 1.5:1)
7d, R = H (n.d., **B**)
(complex mixture)

This represents valuable mechanistic information for the Passerini reaction, which most likely proceeds with the concerted formation of the imidate α-adduct rather than having a true nitrilium ion as intermediate.[25] Furthermore, the trityl substituent can be readily removed yielding primary α-acyloxyamides **7**, which are useful building blocks for the synthesis of natural products and bioactive compounds.[2c,d,26]

In conclusion, we report synthesis of *O*-trityl cyanohydrin derivatives under Brønsted acid catalysis using trityl isocyanide as a convenient cyanating reagent. The trityl substituent is a convenient protecting group, making these products useful building blocks for follow-up chemistry. Its removal is readily achieved and can also be performed in the same pot. Importantly, this approach is mechanistically different than conventional cyanohydrin syntheses, and the Passerini addition/fragmentation mechanism does not involve toxic cyanide species. Finally, enantioenriched *O*-trityl cyanohydrins can be obtained via chiral phosphoric acid organocatalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01481.

Optimization data, experimental procedures, spectroscopic characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)
Structure of **3m** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: r.v.a.orru@vu.nl.
*E-mail: e.ruijter@vu.nl.

Notes

The authors declare no competing financial interest.

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(5) Trityl isocyanide was found to be stable in water, 2 M NaOH, and 1 M HCl; see the Supporting Information for details.

(6) Moreover, in contrast with conventional cyanation reagents, the synthesis of trityl isocyanide does not involve metal cyanides (it is based on conversion of triphenylmethanol to trityl formamide followed by dehydration, see ref 4).

(7) Brønsted acid catalysis is often incompatible with cyanohydrin syntheses due to deactivation of cyanide nucleophiles by formation of HCN. A number of recent papers describe cooperative Brønsted acid—Lewis base catalysis in cyanohydrin synthesis: (a) Ishihara, K.; Ogura, Y. *Org. Lett.* **2015**, *17*, 6070. (b) Ogura, Y.; Akakura, M.; Sakakura, A.; Ishihara, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8299.

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(9) A different mechanism may operate in this case.

(10) To the best of our knowledge, there is only one report describing tritylated cyanohydrins: Cainelli, G.; Panunzio, M.; Contento, M.; Giacomini, D.; Mezzina, E.; Giovagnoli, D. *Tetrahedron* **1993**, *49*, 3809.

(11) A drawback of this strategy is however the low atom economy.

(12) Triphenylacetonitrile coelutes with some *O*-trityl cyanohydrins. Purity of all isolated products is >90%.

(13) The acid activation is essential for the reaction; in the presence of Na_2CO_3, the reaction does not proceed.

(14) A covalent bond between diphenyl phosphate and tritylium is possible, but the trityl transfer necessarily has the free carbocation as intermediate; trityl phosphates have been recently shown to be latent tritylium sources, see: Lv, J.; Zhang, Q.; Zhong, X.; Luo, S. *J. Am. Chem. Soc.* **2015**, *137*, 15576.

(15) Compound **3a** was found to be stable to hydrolysis under the reaction conditions (10 mol % DPP, toluene, 50 °C, 5 h with 2 equiv of water), so **4a** originates exclusively from isocyanide addition.

(16) Conversion of DPP-Tr to DPP (100%, ^{31}P NMR) and 62% conversion of **4a** to **3a** (hydrolysis of DPP-Tr also occurs).

(17) Indeed, small amounts of triphenylmethanol are detected during the reaction.

(18) Plausibly water is also bound to DPP through hydrogen bonding. See: Dong, N.; Zhang, Z.-P.; Xue, X.-S.; Li, X.; Cheng, J.-P. *Angew. Chem.* **2016**, *128*, 1482.

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(20) Only 5% hydrolysis to TrOH occurred while stirring trityl isocyanide with catalytic DPP at 50 °C for 5 h (no TrCN).

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(23) The absolute configuration of **3m** was assigned by X-ray diffraction and chiral HPLC (for details, see the Supporting Information); the configuration of **3a** was assigned by analogy with **3m**.

(24) This is primarily due to an improved trityl transfer (**4m** to **3m**); the intriguing role of the phosphoric acid catalyst in this step is currently under investigation.

(25) The concerted mechanism is generally accepted; however there is also support for the nitrilium ion intermediate: (a) Ramozzi, R.; Morokuma, K. *J. Org. Chem.* **2015**, *80*, 5652. (b) Maeda, S.; Komagawa, S.; Uchiyama, M.; Morokuma, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 644.

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